22 Czeizel AE. Hungarian surveillance of germinal mutations. *Hum Genet* 1989;82:359-66.
23 Czeizel AE. Some epidemiological characteristics of Down's syndrome in Hungary. *Acta Morphol Hung* 1988;36:63-77.
24 Subcommittee for the Study of Endemic Goitre and Iodine Deficiency of the European Thyroid Association. Goitre and iodine deficiency in Europe. *Lancet* 1985;i:1289-93.
25 Delange F, Bürgi H. Iodine deficiency disorder in Europe. *Bull World Health Organ* 1989;67:317-25.
26 Delange F, Heldemann P, Bourdoux P, Larsson A, Vigneri R, Klett M, *et al.* Regional variations of iodine nutrition and thyroid function during neonatal period in Europe. *Biol Neonate* 1986;49:322-30.
27 Fialkow PJ. Thyroid autoimmunity and Down's syndrome. *Ann N Y Acad Sci* 1970;171:500-11.
28 Torffs CP, Berg van den BJ, Oechsli FW, Christianson RE. Thyroid antibodies as a risk factor for Down syndrome and other trisomies. *Am J Hum Genet* 1990;47:727-34.
29 Kochupillaia N, Verma IC, Grewal MS. Remalinggaswami V. Down's syndrome and related abnormalities in an area of high background radiation in coastal Kerälä. *Nature* 1976;262:60-1.
30 High Background Radiation Research Group. Health survey in high background radiation areas in China. *Science* 1980;209:877-80.
31 Hansmann I, Beermann F, Hummler E, Theuring F. Aneuploidy in man and mechanisms of nondisjunction inferred from studying Djungarian hamster oocytes. In: Sharma T, ed. *Trends in chromosome research*. Berlin: Springer, 1990:165-89.
32 Czeizel AE, Elek C, Gundy S, Métneki J, Nemes E, Reis A, *et al.* Environmental trichlorfon and cluster of congenital abnormalities. *Lancet* 1993;341:539-42.
33 Janerich DT, Jacobson HI. Seasonality in Down syndrome. An endocrinological explanation. *Lancet* 1977;i:515-6.
34 Jorgbloet PH, Mulder AM, Hamers AV. Seasonality of pre-ovulatory nondisjunction and the aetiology of Down syndrome. A European collaborative study. *Hum Genet* 1982;62:134-8.
35 German J. Mongolism, delayed fertilization and human sexual behaviour. *Nature* 1968;217:516-8.
36 Sperling K. Frequency and origin of chromosome abnormalities in man. In: Obe G, ed. *Mutations in man*. Berlin: Springer, 1984:128-46.

(Accepted 6 April 1994)

Late deaths and survival after childhood cancer: implications for cure

C M Robertson, M M Hawkins, J E Kingston

Abstract

***Objectives*—To investigate causes of death and survival in subjects who had survived at least five years after diagnosis of childhood cancer; to compare observed mortality with that expected in the general population; and to compare results with a corresponding cohort diagnosed earlier.**

***Design*—Retrospective cohort study.**

***Setting*—Population based National Register of Childhood Tumours.**

***Subjects*—9080 five year survivors of childhood cancer diagnosed in Britain during 1971-85, of whom 793 had died. Comparison with corresponding cohort diagnosed during 1940-70.**

***Main outcome measures*—Cause of death established from all available sources of information (including hospital and general practitioner records and postmortem reports) and underlying cause of death coded on death certificate.**

***Results*—Of the 781 deaths for which sufficient information was available, death was attributed to recurrent tumour in 578 (74%) cases, treatment related effect in 121 (15%), second primary tumour in 52 (7%), and other causes in 30 (4%). Comparison of observed mortality with that expected in the general population indicated a fourfold excess of deaths from non-neoplasic causes. The risk of dying of recurrent tumour in the next 10 years after surviving five years from diagnosis during 1940-70 and 1971-85 fell from 12% to 8%. The risk of dying from a treatment related effect increased slightly from 1% to 2%.**

***Conclusion*—Improvements in five year survival after childhood cancer have been accompanied by a reduction in risk of dying from recurrent tumour during the subsequent 10 years and by a slight increase in risk of dying from treatment related effects. The results provide information relevant to decisions concerning balance between effective treatments and their potentially harmful effects.**

University of Oxford, Childhood Cancer Research Group, Oxford OX2 6HJ
C M Robertson, *senior registrar in community paediatrics*
M M Hawkins, *epidemiologist*

St Bartholomew's Hospital, London EC1
J E Kingston, *consultant paediatric oncologist*

Correspondence to:
Dr Hawkins.

BMJ 1994;309:162-6

Introduction

Survival after childhood cancer has dramatically improved over recent decades, with many diagnostic groups now showing a five year survival rate of at least 60%.[1] This has resulted from increasing use of intensive chemotherapy combined with other modalities of treatment, improved generalised supportive management, and increased centralisation of care. With increasing numbers of long term survivors, the long term effects of treatment for childhood malignancy must be carefully monitored because these will become increasingly important in determining future treatment protocols.

Patients who survive at least five years after childhood cancer experience an excess of deaths compared with the general population.[2] The Childhood Cancer Research Group examined cause of death after five year survival in a cohort of children treated for cancer before 1971 and found excess mortality from certain causes and preventable deaths.[3] Children treated more recently would probably show different patterns of mortality because of the improvements in survival and modern treatment regimens, in which chemotherapy is used more extensively. A recent study of causes of death in all patients (not just five year survivors) who had been treated for non-Hodgkin's lymphoma showed that there was considerable mortality related to treatment, of which a substantial proportion was related to chemotherapy.[4]

The objectives of this study were, firstly, to determine the causes of deaths of children treated for cancer during 1971-85 who had survived at least five years and to relate the causes of death to type of tumour and treatment; secondly, to compare the observed mortality from specific causes with that expected in the general population to identify any departure from the expected pattern of mortality; and thirdly, to compare these results with those from our previous study of late deaths[3] to detect any differences in the pattern of late mortality after treatment in 1940-70 and 1971-85. By investigating the proportion of patients dying of recurrent tumour at specified times after five year survival, we hoped to clarify the extent to which different childhood neoplasms have proved curable in the two periods of diagnosis.

Methods

The National Register of Childhood Tumours, maintained by the Childhood Cancer Research Group in Oxford, has been routinely notified of tumours occurring in children aged under 15 years since 1962 through the national cancer registration scheme operating in Britain. This provides, within the limits of completeness of registration, a population based series of childhood cancer cases. From this series we selected patients who had cancer diagnosed between 1971 and 1985 and who had survived at least five years after diagnosis. All diagnoses from the Birch and Marsden classification[5] apart from Langerhan cell histiocytosis

were included. The cohort was followed up until the end of 1990; deaths occurring after this point were ignored. This period of diagnosis was studied as it followed immediately after our previous study of children diagnosed between 1940 and 1970.[3]

For deaths occurring more than five years after diagnosis we tried to obtain details of the circumstances leading to death and to establish the precise underlying cause of death. The main sources of information were the files held at the National Register of Childhood Tumours and included death certificates, cancer registrations, United Kingdom Children's Cancer Study Group registrations and follow up forms, and abstractions from general practitioners' notes and hospitals' notes. When the information in the files was inadequate we obtained further information from hospital notes, postmortem reports, and in a few cases by direct questions to the consultant responsible for the care of the relevant child.

For each death we assigned the underlying cause, based on all available information, to one of the following broad categories: recurrent tumour, treatment related cause (other than second primary tumour), second primary tumour, accident or trauma, medical condition not related to the tumour or its treatment, or insufficient information. In addition, we recorded the *International Classification of Diseases*, eighth and ninth revisions,[6,7] code for the underlying cause of death on the death certificate, as coded by the Office of Population Censuses and Surveys for England and Wales and by the General Register Office for Scotland.

We adopted certain conventions in assigning deaths to the above categories. Bronchopneumonia was frequently given as the cause of death for patients who had gradually deteriorated with recurrent tumour; these deaths were all coded as recurrent tumour deaths rather than infection. Treatment related deaths were defined as a death where treatment was considered to be the major contributing factor to the death but not necessarily the only factor: if a child died from infection while receiving chemotherapy or within six months of completing treatment or within a year of a bone marrow transplantation the death was coded as treatment related. When death occurred from any cause and there was insufficient evidence to determine whether the patient had active disease at the time the death was coded to insufficient information.

We examined survival to each particular event of interest (death from recurrent tumour or a treatment related cause) with standard life table techniques.[8] When analysing survival to a particular cause of death we regarded all other causes of death as losses to follow up. Mortality from specific causes of death among survivors was compared with that expected in the general population of England and Wales (Office of Population Censuses and Surveys, unpublished report). Expected numbers were estimated by accumulating the person years at risk within strata (defined by sex, age, and calendar period) and multiplying the total person years by the corresponding population mortality. Observed and expected numbers of deaths were compared with exact Poisson methods.[9,10] For this comparison it was necessary to rely on death certificates alone for information on observed deaths because the general population mortality was based on death certificates.

To provide an accurate comparison we carried out new parallel analyses of the two cohorts of five year survivors diagnosed in 1940-70 and 1971-85. We used life table methods to estimate the percentage of patients who survived to five years after diagnosis during 1962-70 and 1971-85; only records relating to patients surviving at least three years were available for patients diagnosed before 1962. We also used life table analyses to estimate the percentage of five year survivors diagnosed in 1940-70 and 1971-85 who died of recurrent tumour or a treatment related cause within the subsequent 10 years.

Results

Of the 9080 five year survivors of childhood neoplasms diagnosed in 1971-85 who were eligible for the analysis, 793 had died by 1990. Death certificates were obtained for 789 of the deaths, hospital notes for 334, postmortem reports for 90, and general practitioner notes for 533. Table I shows that there was insufficient information available to code the cause of 12 deaths; of the remaining 781 deaths, 578 (74%) were attributed to recurrent tumour and 52 (7%) to second primary tumour. There was considerable variation among the different tumour groups in the proportion of deaths due to a particular cause. Among those who had had a diagnosis of acute lymphoblastic leukaemia, tumours of the central nervous system, malignant bone tumours, or soft tissue sarcomas, over 75% of deaths were due to recurrent tumour. In contrast only 31% of deaths after non-Hodgkin's lymphoma were due to recurrent tumour, while 38% resulted from second primary tumours and 31% from a medical condition related to treatment. Other groups for which more than 20% of deaths were attributable to a medical condition related to treatment were those who had had a diagnosis of acute non-lymphoblastic leukaemia, neuroblastoma, or Wilms's tumour.

Table II shows the causes of death during follow up. The most common cause of death during 5-9 years after diagnosis of childhood neoplasm was recurrent tumour, except among survivors of non-Hodgkin's lymphoma, for whom the number of deaths from second primary tumour equalled the number of deaths from recurrent tumour. The most common cause of death among 10 year survivors was still recurrent tumour for all tumours, except for survivors of non-Hodgkin's lymphoma, among whom there were more deaths from second primary tumour, and of Wilms's tumour, for whom treatment related deaths were most common. The proportion of deaths due to causes other than recurrent tumour increased from 145/632 (23%)

TABLE I—*Causes of 793 deaths among 9080 subjects who had survived at least five years after diagnosis of childhood neoplasm in 1971-85. Values are numbers (percentages)* of deaths*

	Childhood neoplasm diagnosed											
Cause of death	Acute lymphoblastic leukaemia (n=2701)	Acute non-lymphoblastic leukaemia (n=138)	Hodgkin's disease (n=726)	Non-Hodgkin's lymphoma (n=450)	Tumour of central nervous system (n=1908)	Neuroblastoma (n=306)	Retinoblastoma (n=426)	Wilms's tumour (n=758)	Malignant bone (n=304)	Soft tissue sarcoma (n=543)	Other neoplasms (n=820)	All neoplasms (n=9080)
Recurrent tumour	275 (78)	6 (67)	30 (61)	5 (31)	155 (78)	11 (61)	5 (63)	10 (50)	23 (79)	28 (76)	30 (71)	578 (74)
Medical condition related to treatment	62 (18)	3 (33)	9 (18)	5 (31)	23 (12)	4 (22)		5 (25)	4 (14)	1 (3)	5 (12)	121 (15)
Second primary tumour	13 (4)		7 (14)	6 (38)	9 (5)	2 (11)	2 (25)	1 (5)	2 (7)	5 (14)	5 (12)	52 (7)
Accident or homicide			2 (4)		5 (3)			2 (10)		1 (3)		10 (1)
Other medical cause (unrelated to tumour or its treatment)	3 (1)		1 (2)		8 (4)	1 (6)	1 (13)	2 (10)		2 (5)	2 (5)	20 (3)
Insufficient information	4				7	1						12
Total deaths	357	9	49	16	207	19	8	20	29	37	42	793

*Based on the 781 deaths with sufficient information to code the cause of death.

during 5-9 years after diagnosis to 41/123 (33%) during 10-14 years and 10/19 (53%) during 15-19 years. The probability of death from recurrent tumour decreased from 6·9% (487/7088) during 5-9 years after diagnosis to 2·3% (82/3622) during 10-14 years and to 0·8% (9/1075) during 15-19 years. These probabilities are approximations calculated with the mean number of survivors in each period as the denominator.

Of the 203 deaths from causes other than recurrent tumour (table I), we obtained hospital notes or post-mortem reports for 183 (90%). Of the 781 deaths to which we could attribute a cause, 20 (3%) were due to medical conditions not directly related to the tumour or its treatment while 121 (15%) were due to medical conditions related to treatment. These 121 treatment related deaths were subcategorised: infections (54), respiratory (13), cardiovascular (11), central nervous system (11), graft versus host disease (7), operative (7), renal (5), gastrointestinal (including hepatic) (5), metabolic or endocrine (3), specific drug toxicity (3), and haemorrhage (2). (Details of these deaths will be given in a separate paper.) Of particular interest were 10 of the 13 respiratory deaths, which were caused by pulmonary fibrosis that occurred after treatment with carmustine, busulphan, or thoracic irradiation; seven of the 11 cardiovascular deaths, which followed treatment with adriamycin; and a further three cardiac deaths which followed thoracic irradiation.

Table III is based on life table estimates and shows the percentage of patients surviving at least five years after diagnosis of childhood neoplasm during 1962-70 and 1971-85 and the percentage of five year survivors with cancers diagnosed in 1940-70 and 1971-85 who subsequently died of recurrent tumour or a treatment related cause in the next 10 years. The proportion of patients surviving five years after diagnosis increased from 26% for those with a diagnosis during 1962-70 to 50% for those with a diagnosis during 1971-85. Of those who survived five years, the proportion dying of recurrent tumour in the next 10 years decreased from 11·5% to 8·3% and the proportion dying from a treatment related cause increased slightly from 0·8% to 1·9%. There was considerable variation in these proportions between the different diagnostic groups. Survivors of acute lymphoblastic leukaemia and of Hodgkin's disease showed the greatest reduction in deaths from recurrent tumour. For acute lymphoblastic leukaemia, this reduction is probably explained by the introduction during 1971-85 of prophylaxis against central nervous system disease, which accounted for many of the deaths from recurrent disease in the earlier period. The reduction in Hodgkin's disease is probably related to the more extensive use of chemotherapy during 1971-85. Among the five year survivors of acute non-lymphoblastic leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, retinoblastoma, and Wilms's tumour diagnosed in 1971-85, no more than 5% died of recurrent tumour during the next 10 years. However, more than 10% of the five year survivors of acute lymphoblastic leukaemia, central nervous system tumours (except for astrocytoma), and Ewing's tumour died from recurrent tumour during the next 10 years.

Table IV is based on information from death certificates only and compares the observed and expected number of deaths from all causes other than neoplasm among five year survivors. The number of non-neoplastic deaths observed was four times higher than expected. The number of observed deaths from

TABLE II—*Causes of death among 9080 subjects who had survived five years after diagnosis of childhood neoplasm in 1979-85 by time after diagnosis. Values are numbers of deaths unless stated otherwise*

		Cause of death 5-9 years after diagnosis						Cause of death 10-14 years after diagnosis						Cause of death 15-19 years after diagnosis					
Childhood neoplasm	No of five year survivors	Recurrent tumour	Treatment*	Second primary tumour	Accident†	Other‡	No of 10 year survivors	Recurrent tumour	Treatment*	Second primary tumour	Accident†	Other‡	No of 15 year survivors	Recurrent tumour	Treatment*	Second primary tumour	Accident†	Other‡	
Acute lymphoblastic leukaemia	2701	244	53	10		2	1377	28	8	2		1	560	3	1	1			
Acute non-lymphoblastic leukaemia	138	6	3				61						18						
Hodgkin's disease	726	23	5	5	1	1	444	7	3	1			178		1	1	1		
Non-Hodgkin's lymphoma	450	5	4	5			232		1	1			81						
Tumour of central nervous system	1908	118	14	6	1	3	1137	32	8	2	3	5	499	5	1	1	1		
Neuroblastoma	306	9	3	2			142	2	1				54						1
Retinoblastoma	426	5		2		1	297						161						
Wilms's tumour	758	9	3	1	1	1	489	1	2			1	223				1		
Malignant bone	304	22	3	2			166	1	1				64						
Soft tissue sarcoma	543	23	1	2	1	2	298	5		3			120						
Other neoplasms	820	23	4	1		2	452	6	1	4			191	1					
All neoplasms	9080	487	93	36	4	12	5095	82	25	13	3	7	2149	9	3	3	3	1	

*Medical condition related to treatment of tumour. †Traumatic death, accident, suicide, or homicide. ‡Other cause unrelated to tumour or its treatment.

TABLE III—*Comparison of five year survival and subsequent death due to recurrent tumour or treatment related cause in patients with childhood neoplasm diagnosed during 1940-70 and 1971-85. Values are actuarial percentages (standard errors)*

	Five year survival after diagnosis		Deaths in 10 years after five year survival			
			Due to recurrent tumour		Due to treatment related cause	
Childhood neoplasm	Diagnosis in 1962-70	Diagnosis in 1971-85	Diagnosis in 1940-70	Diagnosis in 1971-85	Diagnosis in 1940-70	Diagnosis in 1971-85
Acute lymphoblastic leukaemia	8·5 (0·6)	54·2 (0·7)	45·6 (3·9)	12·9 (0·8)	1·7 (1·2)	3·2 (0·4)
Acute non-lymphoblastic leukaemia	2·4 (0·6)	14·2 (1·1)	12·5 (8·3)	5·4 (2·2)	0	4·0 (2·3)
Hodgkin's disease	52·2 (2·5)	85·5 (1·2)	24·6 (2·4)	5·3 (1·0)	3·1 (1·1)	1·6 (0·6)
Non-Hodgkin's lymphoma	18·7 (1·5)	42·8 (1·5)	5·8 (1·6)	1·4 (0·6)	0·5 (0·5)	1·7 (0·8)
Tumours of central nervous system:	37·5 (1·0)	48·2 (0·8)	17·8 (1·1)	10·8 (0·9)	1·4 (0·4)	1·8 (0·4)
Ependymona	31·0 (2·9)	39·1 (2·2)	24·9 (3·9)	11·0 (3·0)	1·8 (1·3)	3·2 (1·6)
Astrocytoma	55·5 (1·8)	63·9 (1·2)	12·4 (1·3)	8·3 (1·1)	0·3 (0·2)	1·0 (0·4)
Medulloblastoma	19·2 (1·8)	35·1 (1·6)	31·3 (3·6)	18·6 (2·9)	1·6 (1·1)	2·8 (1·3)
Neuroblastoma	18·4 (1·3)	28·7 (1·4)	5·7 (1·5)	6·6 (2·4)	0·5 (0·5)	2·4 (1·3)
Retinoblastoma	85·4 (1·9)	88·3 (1·4)	1·3 (0·5)	1·3 (0·6)	0	0
Wilms's tumour	34·8 (1·8)	71·2 (1·4)	1·9 (0·7)	1·8 (0·6)	0·3 (0·3)	1·0 (0·5)
Malignant bone:	21·9 (2·0)	33·2 (1·5)	14·0 (2·8)	8·9 (1·8)	0·8 (0·8)	1·9 (1·0)
Osteosarcoma	17·3 (2·3)	30·1 (2·0)	8·2 (3·2)	5·8 (2·2)	1·5 (1·5)	2·5 (1·5)
Ewing's tumour	23·4 (4·0)	37·0 (2·5)	27·5 (7·1)	13·0 (3·2)	0	1·6 (1·6)
Soft tissue sarcoma:	35·4 (1·9)	47·6 (1·5)	6·6 (1·3)	7·3 (1·4)	0·3 (0·3)	0·2 (0·2)
Rhabdomyosarcoma	24·2 (2·8)	44·3 (1·8)	6·9 (2·7)	6·3 (1·7)	0	0·4 (0·4)
Fibrosarcoma	63·2 (3·8)	60·1 (3·8)	5·2 (1·7)	5·8 (2·6)	0·6 (0·6)	0
All neoplasms	25·9 (0·4)	50·4 (0·4)	11·5 (0·5)	8·3 (0·4)	0·8 (0·1)	1·9 (0·2)

TABLE IV—*Comparison of observed and expected deaths from non-neoplastic causes after five year survival after diagnosis of childhood neoplasm. Values are numbers of observed deaths/numbers of expected deaths (95% confidence interval) unless stated otherwise*

Childhood neoplasm	Infections and parasitic diseases	Endocrine, nutritional, and metabolic diseases and immunity disorders	Diseases of nervous system and sense organs	Diseases of circulatory system	Diseases of respiratory system	Diseases of digestive system	Diseases of genitourinary system	Congenital abnormalities	Medical misadventure	Other accidents	Suicide	Uncertain whether accident, suicide, or homicide	Other	All causes
Acute lymphoblastic leukaemia:														
No of observed deaths	10	0	0	0	5	1	1	0	1	0	0	0	3	21
Observed/expected	83 (40 to 154)				19 (6 to 45)	14 (0·3 to 76)	31 (0·8 to 173)		182 (5 to 1011)				10 (2 to 30)	4 (3 to 7)
Acute non-lymphoblastic leukaemia:														
No of observed deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hodgkin's disease														
No of observed deaths	0	0	2	1	2	0	0	0	0	1	1	0	1	8
Observed/expected			12 (2 to 44)	7 (0·2 to 36)	19 (2 to 67)					1 (0·02 to 4)	3 (0·08 to 18)		7 (0·2 to 38)	3 (1·3 to 6)
Non-Hodgkin's lymphoma														
No of observed deaths	0	0	1	0	0	0	0	0	0	0	0	0	0	1
Observed/expected			12 (0·3 to 68)											1 (0·02 to 5)
Tumours of central nervous system:														
No of observed deaths	0	3	1	2	9	1	1	1	1	5	0	0	2	26
Observed/expected		19 (4 to 54)	3 (0·07 to 15)	6 (0·8 to 23)	36 (17 to 69)	13 (0·3 to 71)	30 (0·8 to 168)	4 (0·1 to 23)	179 (5 to 996)	2 (0·7 to 5)			7 (0·8 to 24)	5 (3 to 7)
Neuroblastoma:														
No of observed deaths	0	1	0	1	1	0	0	0	0	0	0	0	1	4
Observed/expected		56 (1·4 to 312)		50 (1·3 to 276)	45 (1·2 to 253)								45 (1·1 to 252)	11 (3 to 27)
Retinoblastoma:														
No of observed deaths	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Observed/expected		26 (0·7 to 147)												1 (0·03 to 7)
Wilms's tumour:														
No of observed deaths	0	0	1	0	1	0	0	0	0	2	0	0	0	4
Observed/expected			8 (0·2 to 42)		12 (0·3 to 68)					3 (0·3 to 10)				3 (0·7 to 7)
Malignant bone:														
No of observed deaths	1	0	0	0	0	0	1	0	0	0	0	0	0	2
Observed/expected	65 (2 to 361)						181 (5 to 1010)							2 (0·3 to 8)
Soft tissue sarcoma:														
No of obseved deaths	0	0	0	0	2	0	0	0	0	1	0	1	0	4
Observed/expected					33 (4 to 118)					2 (0·04 to 9)		14 (0·4 to 77)		3 (0·9 to 8)
Other neoplasms:														
No of observed deaths	0	1	0	2	1	0	0	0	0	0	0	0	0	4
Observed/expected		16 (0·4 to 89)		17 (2 to 60)	11 (0·3 to 59)									2 (0·6 to 6)
All neoplasms:														
No of observed deaths	11	6	5	6	21	2	3	1	2	9	1	1	7	75
Observed/expected	25 (12 to 44)	9 (3 to 19)	3 (1·03 to 7)	5 (2 to 11)	20 (13 to 31)	6 (0·8 to 23)	23 (5 to 66)	0·9 (0·02 to 5)	85 (10 to 308)	0·9 (0·4 to 2)	0·5 (0·01 to 3)	0·8 (0·02 to 5)	6 (2 to 12)	4 (3 to 5)

infections was 25 times higher than expected and all but one death occurred among survivors of acute lymphoblastic leukaemia. There was a 20-fold excess of respiratory deaths and a fivefold excess of cardiovascular deaths. When all diagnostic groups were considered together there was no evidence of an excess of deaths from suicide or non-medical accidents. Survivors of acute lymphoblastic leukaemia experienced four times the expected number of deaths: in particular there were 83 times the expected number of deaths from infection and 19 times the expected number of deaths from respiratory causes. Survivors of central nervous system tumours experienced five times the expected number of deaths; in particular, there were 36 times the expected number of respiratory deaths. The other excesses seen in table IV arose from a variety of different causes, and no systematic pattern emerged.

Discussion

Comparison of patients with childhood cancer diagnosed in 1962-70 and 1971-85 confirms that there have been great improvements in survival: five year survival after all childhood neoplasms increased from 26% in the first period to 50% in the second. Of those surviving at least five years, the proportion dying of recurrent tumour during the subsequent 10 years decreased from 12% after a diagnosis in 1940-70 to 8% after a diagnosis in 1971-85, while the proportion dying of a treatment related cause increased only slightly, from 1% to 2%. Follow up beyond 15 years from diagnosis is needed to determine whether more recently introduced chemotherapy is associated with adverse outcomes in the longer term.

To our knowledge the only other published study of late deaths in children treated for cancer during the era of modern treatment involving chemotherapy, which began in Britain around 1970, is a relatively small clinical series.[11] A study of late deaths after treatment during 1945-74 from America[12] showed a similar excess mortality to that identified among British five year survivors diagnosed during 1940-70.[3] We have not described deaths from second primary tumours in detail because these will be discussed in a subsequent paper; the patterns and incidence of second primary tumours among survivors of childhood cancer are described elsewhere.[13,14]

TREATMENT RELATED DEATHS

Some might consider that our definition of treatment related death was too broad. In particular, infective deaths that occurred while patients were still receiving treatment might be regarded as deaths from recurrent tumour since this was the reason for their treatment. Despite our broad definition of treatment related death, however, the risk of such deaths among five year survivors was still small, particularly when compared with the risk of death from recurrent tumour.

Of the 121 treatment related deaths, at least 96 occurred in patients who had undergone treatment for recurrent or persisent disease, and the deaths were therefore probably unavoidable. Some of the remaining 25 deaths may have been avoidable, including six deaths from doxorubicin cardiomyopathy, six from pulmonary fibrosis, and four from other radiation effects. It is now well recognised that late manifestations of anthracycline cardiotoxicity occur.[15,16] The figures in this study are likely to be an underestimate of the mortality from this cause as the follow up was relatively short, particularly for the more recent diagnoses. Pulmonary fibrosis continues to be a cause of treatment related mortality, with chemotherapy now emerging as an associated factor as well as radiotherapy. Four of the patients who died from pulmonary fibrosis after treatment with carmustine

Clinical implications

- During recent decades survival to five years after diagnosis of childhood cancer has greatly improved, but little is known about subsequent survival
- We studied over 9000 patients who had survived five years after a diagnosis of childhood neoplasm in 1971-85 and compared them with over 4000 patients who had survived at least five years after diagnosis in 1940-70
- There was considerable improvement in survival to five years and, in the subsequent 10 years, a substantial reduction in the risk of death from recurrent cancer and slightly increased risk of death from an adverse effect of treatment
- Recurrent tumour remained the largest single cause of death among the five year survivors, and mortality from non-neoplastic causes was four times higher than in the general population
- Although increased mortality from treatment is of concern, the risk is greatly outweighed by the danger of recurrent cancer; therefore the primary aim should remain the development of treatments that reduce the risk of recurrent cancer

have previously been reported.[17] Of the six deaths (including two patients who had undergone treatment for recurrent disease) from other radiation effects, four were related to effects on the cardiovascular system and two were related to intra-abdominal fibrosis. Deaths from infection accounted for a large proportion of the treatment related deaths. Although most of these deaths occurred in children who were still being treated or who had recently been treated for relapse, some of these deaths were possibly avoidable. In particular, the deaths from measles, varicella, pneumocystis, and overwhelming sepsis after splenectomy might have been avoided.

It is of concern that the risk of treatment related deaths increased, but it is important to note that the greatest risk of death after five year survival remained recurrent tumour, which accounted for 77% of the deaths during five to nine years after diagnosis, 67% during 10-14 years, and 47% during 15-19 years. Therefore, although it is important to reduce avoidable treatment related mortality, the primary aim should remain the development of treatments that reduce the number of deaths from recurrent tumour among five year survivors.

Limitations of study—This study provided information on the causes of late death after particular types of childhood cancer in Britain. However, most of the cases recorded in the National Register of Childhood Tumours include only crude information on treatment. In particular, there is no record of the specific drugs used in treatment. Thus, we were unable to estimate the risk of specific causes of death in relation to type of treatment received. In particular, although the risk of death from anthracycline related cardiomyopathy within 10 years was small for the whole cohort of five year survivors, we have no means of identifying the subgroups of patients exposed to anthracyclines. In addition, most of the cases recorded in the register have no details of history of relapse or recurrence, and it is therefore not possible to examine the risk of particular causes of death among survivors who do not have a relapse.

CONCLUSION

Our studies, being mainly population based, are unique in providing information on the long term prospects of cure and the risks of dying from particular causes for all patients treated for childhood cancer in Britain. It is well known that there have been great improvements in five year survival after childhood cancer, but the question of what happens thereafter has rarely been investigated. Our results are encouraging in that the substantial improvement in five year survival was not accompanied by a substantially increased subsequent risk of death from recurrent tumour or a treatment related cause. Continued monitoring of these survivors of childhood cancer is important as unforeseen excesses of mortality might emerge. Such studies of mortality reveal the fatal long term risks of childhood cancer and its treatment and such risks are becoming increasingly important in guiding decisions about future treatments.

We thank the consultants who provided much of the information on which this paper is based; the United Kingdom Childrens Cancer Study Group for its support; the consultants who made comments on early drafts of this paper; Michael Potok, Elizabeth Mowat, Maureen Allen, Pat Brownbill, Dave Winter, Hazel Burton, and other members of the Childhood Cancer Research Group for their help with this work; and our colleagues Charles Stiller and Gerald Draper for their support and advice. Our long term follow up study is supported by the Cancer Research Campaign and Leukaemia Research Fund. The Childhood Cancer Research Group is supported by the Department of Health and the Scottish Home and Health Department. This work would have been impossible without the help of the Office of Population Censuses and Surveys (particularly the NHS central register), the Information Services Division of the Common Services Agency of the Scottish Health Service, the Registrar General for Scotland, and the regional cancer registries.

1 Stiller CA, Bunch KJ. Trends in survival of childhood cancer in Britain diagnosed 1971-85. *Br J Cancer* 1990;62:806-15.
2 Hawkins MM. Long term survival and cure after childhood cancer. *Arch Dis Child* 1989;64:798-807.
3 Hawkins MM, Kingston JE, Kinnier Wilson LM. Late deaths after treatment for childhood cancer. *Arch Dis Child* 1990;65:1356-63.
4 Robertson CM, Stiller CA, Kingston JE. Causes of death in children diagnosed with non-Hodgkin's lymphoma bertween 1974 and 1985. *Arch Dis Child* 1992;67:1378-83.
5 Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer* 1987;40:620-4.
6 World Health Organisation. *Manual of the international statistical classification of diseases, injuries and causes of death.* 8th rev ed. Geneva: WHO, 1965.
7 World Health Organisation. *Manual of the international statistical classification of diseases, injuries and causes of death.* 9th rev ed. Geneva: WHO, 1977.
8 Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977;35:1-39.
9 Breslow NE, Day NE. *Statistical methods in cancer research.* Vol 2. *The design and analysis of cohort studies.* Lyons: International Agency for Research on Cancer, 1987.
10 Coleman M, Douglas A, Hermon C, Peto J. Cohort study analysis with a FORTRAN computer program. *Int J Epidemiol* 1986;15:134-7.
11 Al-Asiri RH, Mott MG, Oakhill A. Causes of death in a paediatric oncology unit. *Med Pediatr Oncol* 1992;20:315-20.
12 Nicholson HS, Fears TR, Byrne J. Death during adulthood in survivors of childhood and adolescent cancer. *Cancer* 1994;73:3094-102.
13 Hawkins MM, Draper GJ, Kingston JE. Incidence of second primary tumours among childhood cancer survivors. *Br J Cancer* 1987;56:339-47.
14 Kingston JE, Hawkins MM. Draper GJ, Marsden HB, Kinnier Wilson LM. Patterns of multiple primary tumours in patients treated for cancer during childhood. *Br J Cancer* 1987;56:331-8.
15 Lipshultz SE, Colan SD, Gelber RD, Perez-Ataayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukaemia in childhood. *N Engl J Med* 1991;324:808-15.
16 Steinherz LJ, Steinherz PG, Tan CTC, Heller G, Murphy L. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 1991;226:1672-7.
17 O'Driscoll BR, Haselton PS, Taylor PM, Poulter LW, Gattamaneni HR, Woodcock AA. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med* 1990;323:378-82.

(Accepted 27 April 1994)